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# Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial

**Ramón C. Hermida [1]*, Juan J. Crespo[1,2], Manuel Domínguez-Sardiña[2], Alfonso Otero[3], Ana Moyá[4], María T. Ríos[1,2], Elvira Sineiro[1,4], María C. Castiñeira[1,5], Pedro A. Callejas [1,2], Lorenzo Pousa[1,2], José L. Salgado[1,2], Carmen Durán[2], Juan J. Sánchez[1,6], José R. Fernández[1], Artemio Mojón[1], and Diana E. Ayala[1]; for the Hygia Project Investigators†**

[1]Bioengineering & Chronobiology Laboratories, Atlantic Research Center for Information and Communication Technologies (AtlantTIC), University of Vigo, E.I. Telecomunicación, Campus Universitario, Vigo 36310, Spain; [2]Estructura de Xestión Integrada de Vigo, Servicio Galego de Saúde (SERGAS), Vigo 36214, Spain; [3]Servicio de Nefrología, Complejo Hospitalario Universitario, Estructura de Xestión Integrada de Ourense, Verín e O Barco de Valdeorras, Servicio Galego de Saúde (SERGAS), Ourense 32005, Spain; [4]Estructura de Xerencia Integrada Pontevedra e O Salnés, Servicio Galego de Saúde (SERGAS), Pontevedra 36156, Spain; [5]Estructura de Xestión Integrada de Lugo, Cervo e Monforte de Lemos, Servicio Galego de Saúde (SERGAS), Lugo 27002, Spain; and [6]Estructura de Xestión Integrada de Santiago de Compostela, Servicio Galego de Saúde (SERGAS), Santiago de Compostela 15701, Spain

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**Aims** The Hygia Chronotherapy Trial, conducted within the clinical primary care setting, was designed to test whether bedtime in comparison to usual upon awakening hypertension therapy exerts better cardiovascular disease (CVD) risk reduction.

**Methods and results** In this multicentre, controlled, prospective endpoint trial, 19 084 hypertensive patients (10 614 men/8470 women, 60.5 ± 13.7 years of age) were assigned (1:1) to ingest the entire daily dose of ≥1 hypertension medications at bedtime ($n = 9552$) or all of them upon awakening ($n = 9532$). At inclusion and at every scheduled clinic visit (at least annually) throughout follow-up, ambulatory blood pressure (ABP) monitoring was performed for 48 h. During the 6.3-year median patient follow-up, 1752 participants experienced the primary CVD outcome (CVD death, myocardial infarction, coronary revascularization, heart failure, or stroke). Patients of the bedtime, compared with the upon-waking, treatment-time regimen showed significantly lower hazard ratio—adjusted for significant influential characteristics of age, sex, type 2 diabetes, chronic kidney disease, smoking, HDL cholesterol, asleep systolic blood pressure (BP) mean, sleep-time relative systolic BP decline, and previous CVD event—of the primary CVD outcome [0.55 (95% CI 0.50–0.61), $P < 0.001$] and each of its single components ($P < 0.001$ in all cases), i.e. CVD death [0.44 (0.34–0.56)], myocardial infarction [0.66 (0.52–0.84)], coronary revascularization [0.60 (0.47–0.75)], heart failure [0.58 (0.49–0.70)], and stroke [0.51 (0.41–0.63)].

**Conclusion** Routine ingestion by hypertensive patients of ≥1 prescribed BP-lowering medications at bedtime, as opposed to upon waking, results in improved ABP control (significantly enhanced decrease in asleep BP and increased sleep-time relative BP decline, i.e. BP dipping) and, most importantly, markedly diminished occurrence of major CVD events.

**Trial registration** ClinicalTrials.gov, number NCT00741585.

* Corresponding author. Tel: +34 986 812148, Fax: +34 986 812116, Email: rhermida@uvigo.es

† A complete list of the members of the Hygia Project has been provided elsewhere.[11,17]

**Keywords** Bedtime hypertension chronotherapy • Asleep blood pressure • Ambulatory blood pressure monitoring • Cardiovascular risk • Stroke • Heart failure • Myocardial infarction • Coronary revascularization • Angiotensin-II receptor blockers • Angiotensin-converting enzyme inhibitors

# Introduction

Multiple prospective clinical trials document improved normalization of asleep blood pressure (BP) and 24 h BP patterning—increase in sleep-time relative BP decline towards the more normal dipper profile—when conventionally formulated single and combination hypertension medications are ingested at bedtime than upon awakening,[1,2] without increase in adverse effects.[3] Such administration-time differences in the effects of BP-lowering medications arise from circadian rhythm-dependent influences both on their pharmacokinetics and pharmacodynamics as well as on the mechanisms of BP regulation.[1,4,5] For example, peak activity of the renin–angiotensin–aldosterone system (RAAS) occurs during sleep.[5] Accordingly, bedtime in comparison to upon-waking ingestion of once-a-day formulations of angiotensin-II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs)—as well as their tested combinations with calcium channel blockers (CCBs) and diuretics—results in considerably enhanced reduction in asleep BP mean without compromised therapeutic effect on awake BP.[1,2]

Control of sleep-time BP by proper choice of hypertension *treatment time* is clinically relevant. Findings of numerous independent prospective studies and meta-analyses demonstrate that the asleep BP mean determined by ambulatory BP (ABP) monitoring (ABPM) is a significantly more sensitive prognostic marker of cardiovascular disease (CVD) risk than either daytime office BP measurements (OBPM) or the ABPM-derived awake or 24 h BP mean.[6–11] Most important, outcome studies incorporating periodic ABPM patient assessment during follow-up substantiate therapeutic reduction in the asleep systolic BP (SBP) mean and enhancement of the sleep-time relative SBP decline towards the normal dipper BP pattern lessen CVD risk independent of treatment-induced changes in OBPM and/or wake-time ABP.[8,11]

Despite mounting, although not entirely consistent, evidence documenting the influence of hypertension treatment time on BP control, particularly during sleep,[1,2] few long-term outcomes' studies—including the Heart Outcomes Prevention Evaluation (HOPE),[12] Syst-Eur,[13] Syst-China,[14] and Controlled Onset Extended-Release (COER) Verapamil Investigation of Cardiovascular Endpoints (CONVINCE)[15]—specifically assessed the effects of evening/bedtime ingestion of hypertension medications on CVD risk reduction. However, these investigations, entailing an evening therapeutic strategy of ramipril, nitrendipine, and COER verapamil, were conducted in the absence of a comparative morning-time treatment arm. The Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares (MAPEC; i.e. Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events) study constitutes the first and thus far only reported prospective randomized trial specifically designed to test whether conventionally formulated hypertension medications when routinely ingested at bedtime better reduce CVD risk than when ingested as usual practice upon waking.[16] After the median follow-up of 5.6 years, the bedtime, compared with the upon waking, treatment regimen resulted in significantly enhanced decrease in asleep BP, reduced prevalence of non-dipping, and lower incidence of CVD events.[16] These findings, based on a relatively small cohort of 2156 hypertensive patients, awaited validation in the primary care clinical setting.

The Hygia Project is a research network established to incorporate ABPM as routine procedure to diagnose and manage hypertension, asses response to treatment, and evaluate patient CVD and other risks.[17] Among the multiple ABPM-based studies within the network, we here report the findings of the Hygia Chronotherapy Trial designed to prospectively test the hypothesis of whether ingestion of the entire daily dose of ≥1 hypertension medications at bedtime exerts better ABP control and CVD risk reduction than ingestion of all of them in the morning upon waking.

# Methods

## Organization, management, and quality control

The prospective multicenter Hygia Project was approved by the State Ethics Committee of Clinical Research. Details of its design, management, investigators' training, quality control, safety and compliance assessment, clinical and ABPM procedures, sample size calculations, follow-up, and all other relevant methodological aspects are extensively described elsewhere.[17] In brief, the Hygia Project is composed of a network of 40 primary care centres within the Galician Social Security Health Service [Servicio Galego de Saúde (SERGAS), Northern Spain]. It involves 292 investigators trained and certified in the proper application of ABPM and conduct of study procedures. The Hygia Project is managed by the Research and Coordinating Center (RCC) at the University of Vigo (Spain), which is responsible for all logistic aspects of the Project, including programming and oversight of the electronic data entry booklet (DEB) and the dedicated software for on-line individualized ABPM evaluation and electronic report generation.[17] The software system handling the electronic DEB does not allow incomplete data forms. Clinical site investigators were granted access to the DEB system only after undergoing training by RCC personnel and obtaining certification by the SERGAS. Periodic audit and monitoring standards of the Hygia Project required full verification of informed consent, adherence to inclusion/exclusion criteria, documentation of serious adverse effects, and ascertainment of data for all primary and safety variables.[17]

## Inclusion and exclusion criteria

Participants of the Hygia Chronotherapy Trial represented a population of Caucasian Spanish men and women aged ≥18 years who provided written informed consent for inclusion. Inclusion criteria required each individual adhere to a routine of daytime activity and nighttime sleep. In addition, participants were required to have a diagnosis of hypertension

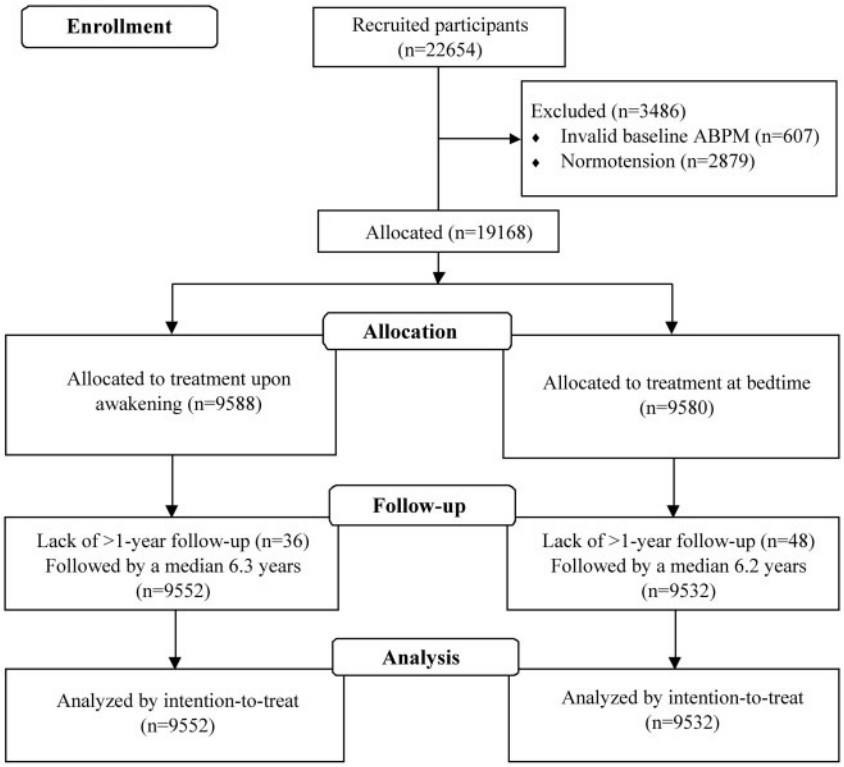



**Figure 1** Flow diagram of participants in the study.

according to the ABP criteria. This entailed evidencing at least one of the following benchmarks: awake SBP mean ≥135 mmHg, awake diastolic BP (DBP) mean ≥85 mmHg, asleep SBP mean ≥120 mmHg, asleep DBP mean ≥70 mmHg, and prescription of BP-lowering treatment,[18,19] as corroborated by 48 h ABPM done upon recruitment mainly to confirm/refute the diagnosis of hypertension inferred by daytime OBPM of untreated individuals or to evaluate BP control in treated hypertensive persons. Additional reasons to request ABPM in the Hygia Project include, among several others and regardless of OBPM, elevated fasting glucose, metabolic syndrome, type 2 diabetes, chronic kidney disease (CKD), previous complications of pregnancy, suspicion/diagnosis of sleep disorders, and age ≥60 years. Exclusion criteria were pregnancy, history of alcoholism or narcotic addiction, night or rotating shift-work employment, acquired immunodeficiency syndrome, secondary hypertension, CVD and certain associated medical conditions (unstable angina pectoris, heart failure, life-threatening arrhythmia, atrial fibrillation, kidney failure, and grade III–IV retinopathy), intolerance to ABPM, and inability to communicate and comply with all study requirements. The minimum targeted median follow-up was 5 years, with a required ≥1-year minimal follow-up per participant.[17]

## Participants, diagnostic criteria, and sample size calculation

Between 2008 and 2018, the participating primary care investigators referred a total of 22 654 persons, with 22 047 providing all required information for study. The other 607 individuals were excluded due to inadequate ABPM sampling at baseline and non-consent for follow-up ABPM evaluations. At the time of recruitment, 2879 participants were normotensive according to the abovementioned ABP criteria and, therefore, excluded from this trial. In addition, 84 participants were disqualified due to less than the required 1-year minimum follow-up. Thus, the final evaluated population for the hypothesis assessed herein is 19 084 (10 614 men/8470 women) hypertensive patients aged 60.5 ± 13.7 (mean ± SD) years (*Figure 1*). Diabetes was defined as fasting glucose ≥126 mg/dL (7.0 mmol/L) on at least two clinical assessments ≥3 months apart in participants without history of diabetes, or prescription of glucose-lowering treatment.[20] The CKD was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 $m^2$, albuminuria [albumin/creatinine (Cr) ratio ≥30 $mg/g_{Cr}$), or both, on at least two occasions ≥3 months apart.[21] eGFR (mL/min/1.73 $m^2$) was estimated by the CKD-EPI (epidemiology collaboration) equation.[22]

For an estimated incidence of ∼20 and ∼40 CVD events/1000 patient-years in the general uncomplicated hypertensive population and in patients complicated with either diabetes or CKD, respectively,[10,13,16,17] at the two-sided level of 5% and with a power of 95%, 10 700 uncomplicated participants and 3800 patients with either of those two medical conditions—a total sample of 18 300 persons—would make possible detection of a reduction in morbidity/mortality of >20% after a median follow-up of ≥5 years in participants allocated to the bedtime vs. upon-waking treatment regimen.

## Study design

The Hygia Chronotherapy Trial was designed as a multicentre, controlled, PROBE (prospective, randomized, open-label, blinded endpoint) study with patients distributed in a 1:1 ratio into two parallel arms defined according to the circadian time of treatment: either ingestion of the entire daily dose of ≥1 prescribed BP-lowering medications of the major therapeutic classes (ARB, ACEI, CCB, β-blocker, and/or diuretic) at bedtime

(bedtime-treatment regimen; $n = 9552$) or ingestion of all of such medications upon awakening (awakening-treatment regimen; $n = 9532$; *Figure 1*). Participating primary care physicians were allowed to prescribe without restriction any BP-lowering medication approved by the Spanish Agency of Medications and Health Products for once-daily dosing from any of the five listed recommended therapeutic classes as first-line therapy for untreated participants and as combination therapy for uncontrolled patients (those above target ABP thresholds). Dual and triple therapies were prescribed, when available, in single-tablet fixed combinations to improve adherence. The protocol required avoiding division of prescribed medications for ingestion as split doses, e.g. one-half upon morning arising and other half at bedtime. Thus, individuals of the bedtime-treatment group ingested the entire daily dose of the medications at this time and not a portion of one or more of them also in the morning.

If, based on the ABPM threshold criteria provided above, the ABP of a given participant remained uncontrolled at any time during follow-up when treated with medication(s) at the maximum recommended dose(s), additional therapy could be added in keeping with current clinical practice guidelines.[19] Accordingly, changes in treatment during follow-up were based on results of periodic ABPM evaluations, regardless of daytime OBPM. Administration-time-dependent difference in effects of other treatments, including statins and diabetes medications, was not an objective of study; they were prescribed as needed and ingested as recommended according to current clinical practice guidelines.[19]

To increase compliance and adherence to the allocated hypertension treatment-time schedule (upon waking or bedtime), participants were instructed upon recruitment and reminded at every clinical visit throughout follow-up to place their prescribed medications on the bedside table and to ingest them, depending on their assigned treatment-time schedule, either immediately upon awakening from night-time sleep or before turning the lights off to retire to sleep at night. Investigators performed the Morisky–Green test[23] at each scheduled ABPM visit during follow-up to assess participant compliance with the prescribed BP-lowering treatment and schedule. In addition, at every follow-up clinical visit, adverse events—including type, duration, seriousness, intensity, and possible relation to hypertension therapy and schedule—were registered when spontaneously reported by the patient and/or revealed through non-direct questioning and physical examination.

## ABP and other assessments

At inclusion and at every scheduled clinic visit throughout follow-up, at least three consecutive OBPM were made on each participant after resting in a seated position for ≥10 min using a validated automatic oscillometric device (HEM-705IT; Omron Health Care Inc., Vernon Hills, IL, USA). Immediately thereafter, ABPM was initiated utilizing a calibrated and validated SpaceLabs 90207 device (SpaceLabs Inc., Issaquah, WA, USA) to measure SBP, DBP, and heart rate every 20 min between 07:00 and 23: 00 h and every 30 min during the night for 48 consecutive hours. The upper arm circumference was measured at each clinic visit to ensure proper cuff size for OBPM and ABP assessment. ABPM was carried out for 48 h, instead of the most usual 24 h, to optimize the reproducibility of results, as accurate determination of ABP characteristics—including mean BP values and dipping classification—and ABPM-based CVD risk appraisal depend markedly on ABPM duration.[24] Individuals were instructed to adhere to usual activities with minimal restrictions, i.e. maintaining a similar activity–rest schedule and avoiding daytime napping during the two consecutive days of evaluation. Participants kept a diary to record, among other information, the time of retiring to bed at night and awakening in the morning. Such individualized information enabled accurate calculation of the awake and asleep BP means of each participant at every evaluation. In keeping with current recommendations,[18] ABP series were considered invalid for analysis and thus necessitating repeated ABPM [4.13% (95% CI 3.92–4.35)] if ≥30% of scheduled measurements were missing, data were lacking for an interval of >2 h or were obtained when the rest–activity schedule was inconsistent during the 2 days of assessment, or the sleep span was <6 or >12 h. ABPM profiles obtained during the course of the Hygia Project were always automatically analysed online utilizing a proprietary system that includes dedicated software for individualized ABPM evaluation (US Patent 8,428,965-B2).[17] The software program analyses the participant's ABPM profile by comparison to circadian (with reference to the rest–activity cycle) time-specified tolerance intervals of SBP, DBP, and heart rate earlier constructed for each sex based on databases derived from previous assessments of normotensive individuals also evaluated by 48-h ABPM.[17] We used the lower reference BP threshold to avert nocturnal hypotension, especially for participants of the bedtime-therapy regimen based on the previous demonstration of stronger reduction in asleep BP mean by hypertension medications when ingested at bedtime than at morning.[1,2] At every clinic visit when ABPM was conducted, morning (between 08:00 and 09: 00 h) urine and blood samples were collected after overnight fasting and immediately analysed by routine automatic techniques at laboratory facilities of the SERGAS in compliance with quality standards.

## Follow-up

The above-described clinical procedures were scheduled yearly, or more often in uncontrolled hypertensive participants and those having compelling clinical conditions of elevated CVD risk—including diabetes, CKD, and past CVD events.[17] Investigators reviewed the complete electronic clinical records of every participant at least annually and at least 1 year following his/her last ABPM evaluation. External non-investigator medical specialists of the corresponding referring tertiary hospital services categorized CVD and other events recorded in the electronic medical history in accordance with defined current diagnostic criteria[17] utilized at all clinical SERGAS centres. The Hygia Project Events Committee, comprised of independent clinicians blinded to medical records, ABPM findings, and treatment scheme of participants, periodically and collegiately evaluated such clinical reports devoid of personal identifiers to ascertain and certify every registered event. These included myocardial infarction, angina pectoris, coronary revascularization, heart failure, peripheral artery disease, retinal artery thrombotic occlusion, haemorrhagic stroke, ischaemic stroke, transient ischaemic attack, and death from all causes. The a priori defined primary CVD outcome for this trial is as follows: myocardial infarction, coronary revascularization, heart failure, ischaemic stroke, haemorrhagic stroke, and CVD death. In keeping with the approved protocol,[17] we also individually analysed the secondary endpoints of stroke, coronary events (CVD death, myocardial infarction, and coronary revascularization), and cardiac events (coronary events and heart failure).

## Statistical methods

The '48 h ABP mean' was calculated using all valid readings of the 48-h assessment. Awake and asleep ABP means were calculated using all valid readings of the actual hours of daytime activity and night-time sleep, respectively, as differentiated by participant diary entries. To avoid confounding by non-equidistant BP sampling on mean values,[18] the 48-h, awake, and asleep spans were each divided into an integer number of classes of identical time length; the respective BP means were then determined as the average of the relevant time-class values. Sleep-time relative BP decline, an index of BP dipping expressed as percentage decrease in mean BP during night-time sleep relative to mean BP during daytime activity, was calculated as follows: [(awake ABP mean - asleep ABP mean)/awake ABP mean] × 100, utilizing all valid data of the 48 h ABPM.

Participants were designated as dipper if the sleep-time relative SBP decline was ≥10% and as non-dipper otherwise.[18,19]

Demographic and clinical variables were compared on an intention-to-treat basis among participants allocated to the two treatment-time regimens by two-sided *t*-test (continuous variables) or non-parametric $\chi^2$ test (proportions). The Cox proportional-hazard model adjusted for significant confounding variables was used to estimate hazard ratios (HR), with 95% CI, for events associated with each treatment-time regimen. Demographic, anthropometric, and clinical laboratory variables of *Table 1* were tested as potential confounding variables by non-automatic (forward and backward) stepwise Cox survival analysis based on the Akaike Information Criterion. Adjustments were finally applied for the significant influential characteristics of age, sex, type 2 diabetes, CKD, smoking, HDL cholesterol, previous CVD event, asleep SBP mean, and sleep-time relative SBP decline, as they were the only ones jointly significant in Cox regression analyses.[11] For survival analysis, follow-up was established as either the interval of time until the first confirmed CVD event or the interval of time to the last review of the clinical records of non-event participants. Survival curves were generated using the Kaplan–Meier product-limit method and compared by the Mantel log-rank test. Statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) and R version 3.3.3 (R Foundation for Statistical Computing).

# Results

## Demographic, clinical, and ABP characteristics according to treatment-time regimen

In keeping with the trial design, there were no statistically significant differences at baseline between the two balanced treatment-time groups in the prevalence of type 2 diabetes, obstructive sleep apnoea, CKD, history of previous CVD events, obesity, and all evaluated anthropometric and clinical laboratory test variables (*Table 1*). Daytime OBPM, average ABP values, and prevalence of non-dipping were also equivalent between groups (*Table 1*). At the conclusion of the study, the number of prescribed hypertension medications (usually each at maximum doses) was slightly but significantly ($P < 0.001$) lower in the bedtime-treatment regimen, resulting in relatively small differences between groups in the percentage of individuals treated with any given class of single or combination therapy (*Table 2*). Analysis correcting for the average number of ingested medications revealed a slightly higher percentage of diuretics and lower percentage of CCBs use by participants of the upon-waking than bedtime-treatment groups. The most frequently prescribed monotherapies across both treatment-time schemes were ARBs (mainly valsartan or telmisartan) or ACEIs (mostly enalapril or ramipril; 69% of participants) and CCBs (mainly amlodipine; 13% of patients). The most commonly prescribed dual combination therapies were ARB/ACEI with diuretic—mostly hydrochlorothiazide in doses up to 25 mg/day—(43%) or CCB (26%). The most used triple therapy was ARB/ACEI–diuretic–CCB (69%). Finally, the proportion of participants of the upon-waking and bedtime-therapy groups prescribed statins (36.8 vs. 38.1%, respectively; $P = 0.064$) and low-dose (100 mg/day) aspirin (25.0 vs. 25.5%; $P = 0.462$) was similar.

At the final evaluation, patients of the bedtime-treatment regimen showed significantly lower creatinine and LDL cholesterol and higher HDL cholesterol and eGFR than those treated upon awakening (*Table 2*). Data of the last ABPM evaluation revealed significantly lower asleep ($P < 0.001$), but not awake, SBP/DBP mean in participants of the bedtime than in those of the awakening-treatment regimen (*Table 2*). The sleep-time relative SBP/DBP decline was significantly greater in those of the bedtime regimen ($P < 0.001$); accordingly, the proportion of patients with the higher CVD risk non-dipper BP pattern was significantly lower with the bedtime treatment than with the upon-waking treatment (37% vs. 50%; $P < 0.001$).

## CVD risk according to treatment-time regimen

During the median follow-up period of 6.3 years (inter-quartile range 4.1–8.3 years), 3246 participants had a listed registered event; of them, 1752 experienced the main CVD outcome (myocardial infarction: 274; coronary revascularization: 302; heart failure: 521; stroke: 345; CVD death: 310; *Figure 2*). Patients of the bedtime-treatment regimen evidenced significantly lower HR of the primary CVD outcome (adjusted by the only significant influential characteristics of age, sex, type 2 diabetes, CKD, smoking, HDL cholesterol, previous CVD event, asleep SBP mean, and sleep-time relative SBP decline) compared with those ingesting all medications upon awakening [HR = 0.55 (95% CI 0.50–0.61), $P < 0.001$; *Figure 2A*]. The substantial beneficial risk reduction with bedtime treatment was also highly significant for the secondary endpoints of stroke, coronary events, and cardiac events analysed separately (*Figure 2A*). Analyses of the influence of hypertension treatment time on each of the registered single event classes further documented significantly better risk reduction with bedtime treatment than with awakening treatment, mainly for CVD death [HR = 0.44 (0.34–0.56), $P < 0.001$], haemorrhagic stroke [0.39 (0.23–0.65), $P < 0.001$], heart failure [0.58 (0.49–0.70), $P < 0.001$], and peripheral artery disease [0.52 (0.41–0.67), $P < 0.001$; *Figure 2B*). Kaplan–Meier survival curves depict the highly significant difference between patients of the two treatment-time groups in CVD event-free interval for CVD outcome (log-rank 140.1; $P < 0.001$; *Figure 3A*) and total CVD events (log-rank 174.0; $P < 0.001$; *Figure 3B*).

Analysis of the impact of hypertension treatment time on CVD outcome for participants further categorized by influential markers of CVD risk indicates significantly lower HR of CVD events when BP-lowering medications were ingested at bedtime regardless of the patient's sex, age, smoking habits, hypertension treatment at baseline, normal/elevated awake or asleep SBP mean, dipper/non-dipper BP pattern, and absence/presence of diabetes, CKD, previous CVD event, or any of these three complications (*Figure 4*). CVD risk reduction associated with the bedtime-treatment regimen was similar regardless of most of the influential variables, although greater benefit was documented for previously untreated individuals than treated participants and those without history of CVD events than those with such history.

## Treatment safety and compliance

There were no treatment-time differences in the prevalence of patients reporting adverse effects at any visit during follow-up (6.7 vs. 6.0% for the awakening and bedtime-treatment regimen, respectively; $P = 0.061$). Poor adherence (Morisky–Green test) was reported at any visit during follow-up by 2.8 and 2.9%, respectively, of patients of the awakening and bedtime-treatment groups

**Table 1 Baseline characteristics of participants categorized according to treatment-time regimen (either upon awakening or at bedtime)**

| Variable | All | Awakening | Bedtime | *P* between groups |
|---|---|---|---|---|
| Demographic and clinical characteristics | | | | |
| Participants, *n* | 19 084 | 9552 | 9532 | |
| Age, years | 60.5 ± 13.7 | 60.5 ± 13.9 | 60.6 ± 13.5 | 0.831 |
| Sex, % men | 55.6 | 56.2 | 55.0 | 0.086 |
| Height, cm | 162.9 ± 9.6 | 163.0 ± 9.7 | 162.8 ± 9.5 | 0.059 |
| Weight, kg | 79.0 ± 15.2 | 78.9 ± 15.3 | 79.0 ± 15.1 | 0.518 |
| BMI, kg/m$^2$ | 29.7 ± 4.8 | 29.6 ± 4.8 | 29.7 ± 4.7 | 0.030 |
| Waist, cm | 101.3 ± 12.2 | 101.2 ± 12.3 | 101.3 ± 12.2 | 0.850 |
| Night-time sleep duration, h | 8.8 ± 1.3 | 8.8 ± 1.4 | 8.8 ± 1.3 | 0.156 |
| Type 2 diabetes, % | 23.9 | 23.7 | 24.1 | 0.484 |
| Obstructive sleep apnoea, % | 4.1 | 4.2 | 3.9 | 0.374 |
| Smoking, % | 15.2 | 15.6 | 14.8 | 0.129 |
| Obesity, % | 43.0 | 42.6 | 43.5 | 0.180 |
| Chronic kidney disease, % | 29.4 | 29.9 | 28.9 | 0.141 |
| Previous CVD events, % | 10.4 | 10.8 | 10.0 | 0.054 |
| Hypertension treatment, % | 57.4 | 57.9 | 56.9 | 0.166 |
| Duration of known hypertension, years | 8.7 ± 8.3 | 8.6 ± 8.3 | 8.8 ± 8.2 | 0.137 |
| Clinical laboratory test values | | | | |
| Glucose, mg/dL | 107.7 ± 32.6 | 107.8 ± 33.1 | 107.6 ± 32.1 | 0.557 |
| Creatinine, mg/dL | 1.06 ± 0.72 | 1.07 ± 0.59 | 1.05 ± 0.84 | 0.060 |
| Uric acid, mg/dL | 5.7 ± 1.6 | 5.8 ± 1.6 | 5.7 ± 1.6 | 0.171 |
| Total cholesterol, mg/dL | 203.7 ± 43.2 | 203.1 ± 43.4 | 204.1 ± 43.1 | 0.086 |
| Triglycerides, mg/dL | 133.0 ± 84.7 | 132.8 ± 86.3 | 133.2 ± 83.1 | 0.738 |
| HDL cholesterol, mg/dL | 53.0 ± 14.8 | 52.8 ± 15.4 | 53.1 ± 14.1 | 0.144 |
| LDL cholesterol, mg/dL | 123.8 ± 37.7 | 123.9 ± 37.8 | 123.8 ± 37.8 | 0.886 |
| Haemoglobin, g/dL | 14.1 ± 1.6 | 14.1 ± 1.6 | 14.1 ± 1.6 | 0.894 |
| Estimated glomerular filtration rate | 79.0 ± 24.7 | 78.6 ± 25.5 | 79.3 ± 24.0 | 0.160 |
| Albumin/creatinine (Cr) ratio, mg/g$_{Cr}$, median (interquartile range) | 6.0 (3.0–16.6) | 6.0 (3.0–15.9) | 6.0 (3.0–17.1) | 0.272 |
| Office[a] and ambulatory BP | | | | |
| Office SBP, mmHg | 149.4 ± 20.1 | 149.4 ± 20.5 | 149.5 ± 19.9 | 0.987 |
| Office DBP, mmHg | 86.1 ± 12.1 | 86.3 ± 11.9 | 86.0 ± 12.3 | 0.276 |
| Office PP, mmHg | 63.3 ± 17.0 | 63.1 ± 17.0 | 63.5 ± 16.9 | 0.351 |
| Office heart rate, beats/min | 72.8 ± 12.3 | 73.1 ± 12.5 | 72.6 ± 12.2 | 0.064 |
| Awake SBP mean, mmHg | 136.0 ± 14.4 | 136.1 ± 14.9 | 135.9 ± 14.0 | 0.449 |
| Asleep SBP mean, mmHg | 123.6 ± 15.2 | 123.3 ± 16.0 | 123.7 ± 14.6 | 0.138 |
| 48 h SBP mean, mmHg | 131.6 ± 13.8 | 131.4 ± 14.4 | 131.7 ± 13.3 | 0.306 |
| Sleep-time relative SBP decline, % | 9.0 ± 7.8 | 9.3 ± 7.9 | 9.0 ± 7.6 | 0.000 |
| Awake DBP mean, mmHg | 81.3 ± 11.3 | 81.3 ± 11.5 | 81.3 ± 11.2 | 0.955 |
| Asleep DBP mean, mmHg | 70.2 ± 10.1 | 70.1 ± 10.2 | 70.3 ± 10.0 | 0.420 |
| 48 h DBP mean, mmHg | 77.4 ± 10.4 | 77.2 ± 10.6 | 77.5 ± 10.3 | 0.104 |
| Sleep-time relative DBP decline, % | 13.3 ± 8.4 | 13.3 ± 8.7 | 13.2 ± 8.2 | 0.468 |
| Non-dipper, % | 49.3 | 49.0 | 49.5 | 0.363 |

Values are shown as mean ± SD, unless otherwise indicated. Obesity: BMI ≥30 kg/m$^2$. Chronic kidney disease: estimated glomerular filtration rate <60 mL/min/1.73 m$^2$, albuminuria, or both, on at least two occasions ≥3 months apart.[21] Glomerular filtration rate (mL/min/1.73 m$^2$) estimated by the CKD-EPI equation.[22] Sleep-time relative BP decline, index of BP dipping, defined as percentage decrease in mean BP during nighttime sleep relative to mean BP during daytime activity, calculated as: [(awake BP mean - asleep BP mean)/awake BP mean] × 100. Non-dipper: individuals with sleep-time relative SBP decline <10%, using data sampled by ABPM for 48 consecutive hours.

[a]Values correspond to the average of at least three conventional morning-time BP measurements obtained per participant at the clinic after resting ≥10 min before initiating 48 h ABPM.

BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; PP, pulse pressure (SBP-DBP); SBP, systolic blood pressure.

**Table 2 Final characteristics of participants categorized according to treatment-time regimen (either upon awakening or at bedtime)**

| Variable | Awakening | Bedtime | *P* between groups |
|---|---|---|---|
| Participants, *n* | 9552 | 9532 | |
| Hypertension treatment | | | |
| Number of medications | 1.80 ± 0.89 | 1.71 ± 0.93 | <0.001 |
| ARB, % | 53.1 | 53.1 | 0.995 |
| ACEI, % | 25.3 | 23.4 | 0.002 |
| CCB, % | 32.7 | 36.8 | <0.001 |
| β-Blocker, % | 22.0 | 17.5 | <0.001 |
| Diuretic, % | 46.5 | 39.5 | <0.001 |
| Clinical laboratory test values | | | |
| Glucose, mg/dL | 108.1 ± 33.5 | 108.3 ± 31.7 | 0.656 |
| Creatinine, mg/dL | 1.16 ± 0.96 | 1.06 ± 0.90 | <0.001 |
| Uric acid, mg/dL | 5.9 ± 1.6 | 5.8 ± 1.5 | 0.057 |
| Total cholesterol, mg/dL | 198.5 ± 40.3 | 197.7 ± 40.6 | 0.385 |
| Triglycerides, mg/dL | 131.7 ± 84.6 | 131.1 ± 80.6 | 0.639 |
| HDL cholesterol, mg/dL | 51.8 ± 15.8 | 53.0 ± 14.8 | <0.001 |
| LDL cholesterol, mg/dL | 120.7 ± 36.6 | 118.2 ± 36.5 | 0.002 |
| Haemoglobin, g/dL | 14.1 ± 1.6 | 14.0 ± 1.6 | 0.270 |
| Estimated glomerular filtration rate | 75.7 ± 26.9 | 79.3 ± 23.5 | <0.001 |
| Albumin/creatinine (Cr) ratio, mg/$g_{Cr}$, median (interquartile range) | 7.0 (3.7–20.0) | 6.5 (3.6–18.0) | 0.030 |
| Office[a] and ambulatory BP | | | |
| Office SBP, mmHg | 143.2 ± 20.9 | 140.0 ± 20.6 | <0.001 |
| Office DBP, mmHg | 82.4 ± 12.3 | 81.4 ± 12.4 | <0.001 |
| Office PP, mmHg | 60.8 ± 17.9 | 58.6 ± 17.9 | <0.001 |
| Office heart rate, beats/min | 71.9 ± 12.5 | 72.4 ± 12.5 | 0.078 |
| Awake SBP mean, mmHg | 129.5 ± 14.7 | 129.2 ± 13.4 | 0.294 |
| Asleep SBP mean, mmHg | 118.0 ± 16.6 | 114.7 ± 14.6 | <0.001 |
| 48 h SBP mean, mmHg | 125.6 ± 14.5 | 124.3 ± 12.9 | <0.001 |
| Sleep-time relative SBP decline, % | 8.5 ± 8.4 | 12.2 ± 7.7 | <0.001 |
| Awake DBP mean, mmHg | 76.7 ± 10.6 | 76.3 ± 10.0 | 0.124 |
| Asleep DBP mean, mmHg | 66.1 ± 10.1 | 64.5 ± 9.3 | <0.001 |
| 48 h DBP mean, mmHg | 73.1 ± 9.9 | 72.2 ± 9.2 | <0.001 |
| Sleep-time relative DBP decline, % | 13.3 ± 9.4 | 15.3 ± 8.6 | <0.001 |
| Non-dipper, % | 50.3 | 37.5 | <0.001 |

Values are shown as mean ± SD, unless otherwise indicated. Sleep-time relative BP decline, index of BP dipping, defined as percentage decrease in mean BP during nighttime sleep relative to mean BP during daytime activity, calculated as: [(awake BP mean - asleep BP mean)/awake BP mean] × 100. Non-dipper: individuals with sleep-time relative SBP decline <10%, using data sampled by ABPM for 48 consecutive hours.

[a]Values correspond to the average of at least three conventional BP measurements obtained per participant in the morning at the clinic after resting ≥10 min before initiating 48-h ABPM.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; PP, pulse pressure (SBP-DBP); SBP, systolic blood pressure.

(*P* = 0.813). Due to strict patient control by periodic ABPM, [17] only 39 and 26 patients of the upon-waking and bedtime groups, respectively (0.3% of all participants; *P* = 0.114 between groups), experienced sleep-time hypotension, defined by current ABPM criteria, [18] at any time during the 6.3-year median follow-up.

## Discussion

The Hygia Chronotherapy Trial is the first outcomes ABPM-based study of meaningful follow-up duration and sufficiently large number of major CVD events conducted within the primary care medical setting to assess prospectively in a large cohort of hypertensive persons diagnosed by ABP criteria the hypothesis of whether ingestion of the entire daily dose of ≥1 BP-lowering medications at bedtime exerts not only better ABP control but also better protection against major CVD events than ingestion of all medications in the morning upon awakening. Results establish, first, greater ABP control in patients of the bedtime treatment than in those of the awakening-treatment regimen. The main differences in ABP control were achievement with bedtime treatment of: (i) significantly lower asleep BP mean

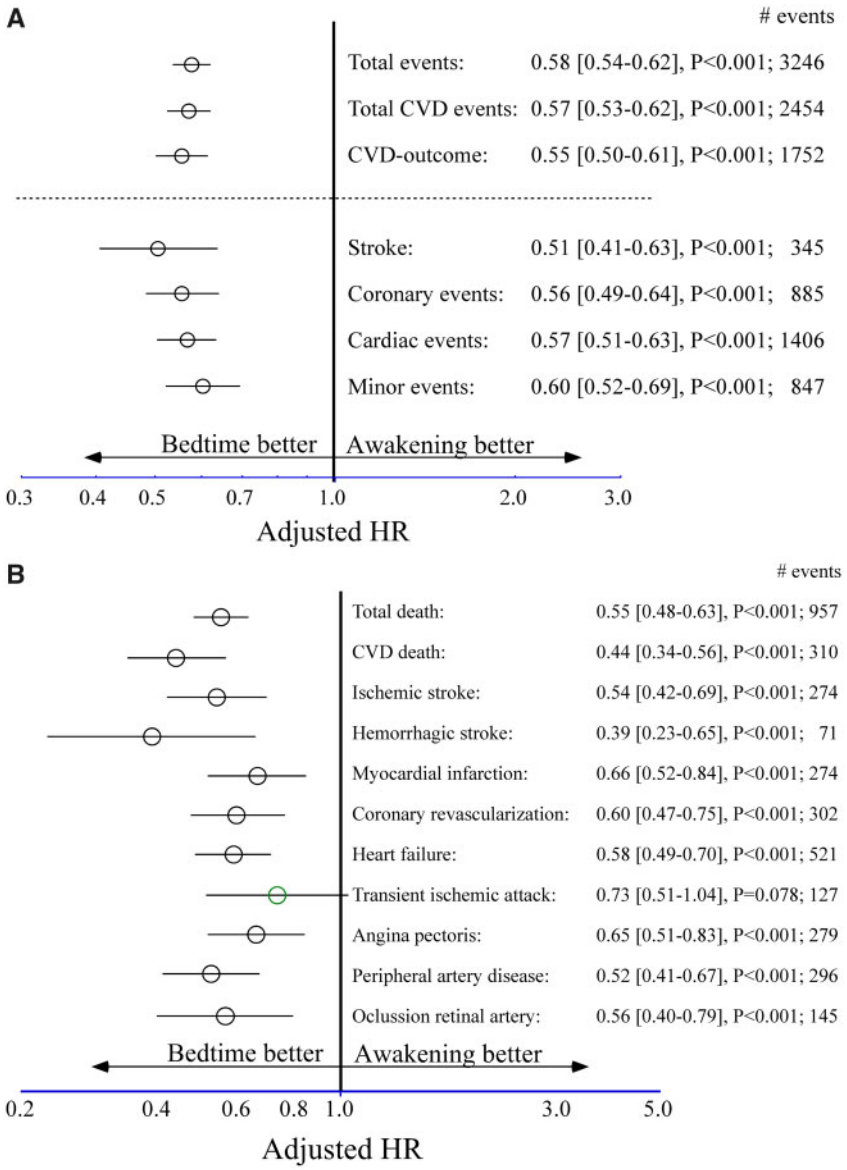



**Figure 2** Adjusted hazard ratio of cardiovascular disease outcome as a function of hypertension treatment-time regimen (either upon awakening or at bedtime). (*A*) Adjusted hazard ratio (95% CI) of primary and secondary composite endpoints. Total events: death from all causes, myocardial infarction, coronary revascularization, heart failure, ischaemic and haemorrhagic stroke, angina pectoris, peripheral artery disease, thrombotic occlusion of the retinal artery, and transient ischaemic attack. Total cardiovascular disease events: cardiovascular disease death, myocardial infarction, coronary revascularization, heart failure, stroke, angina pectoris, peripheral artery disease, and transient ischaemic attack. Cardiovascular disease outcome: cardiovascular disease death, myocardial infarction, coronary revascularization, heart failure, and stroke. Coronary events: cardiovascular disease death, myocardial infarction, and coronary revascularization. Cardiac events: coronary events and heart failure. Minor events: angina pectoris, peripheral artery disease, thrombotic occlusion of the retinal artery, and transient ischaemic attack. (*B*) Adjusted hazard ratio (95% confidence interval) for each evaluated single endpoint. Adjustments were applied for significant influential baseline characteristics of age, sex, type 2 diabetes, chronic kidney disease, smoking, HDL cholesterol, previous cardiovascular disease event, asleep systolic blood pressure mean, and sleep-time relative systolic blood pressure decline.

without loss of awake BP-lowering efficacy (*Table 2*) and (ii) greater sleep-time relative BP decline resulting in a significantly lower prevalence of non-dipping (*Table 2*). These ingestion-time-dependent effects on asleep BP control were strongly associated with substantially attenuated CVD risk. Indeed, progressive decrease in the asleep SBP mean during the 6.3 years of follow-up was the most significant predictor of reduced CVD risk, beyond the prognostic value of other associated conventional risk markers, such as advanced age, male sex, low HDL cholesterol, smoking, type 2 diabetes, and CKD.[11] As documented in most reported prospective chronotherapy trials,[1,2] bedtime hypertension treatment is the simplest strategy for successfully achieving the therapeutic goals of adequate asleep BP reduction/

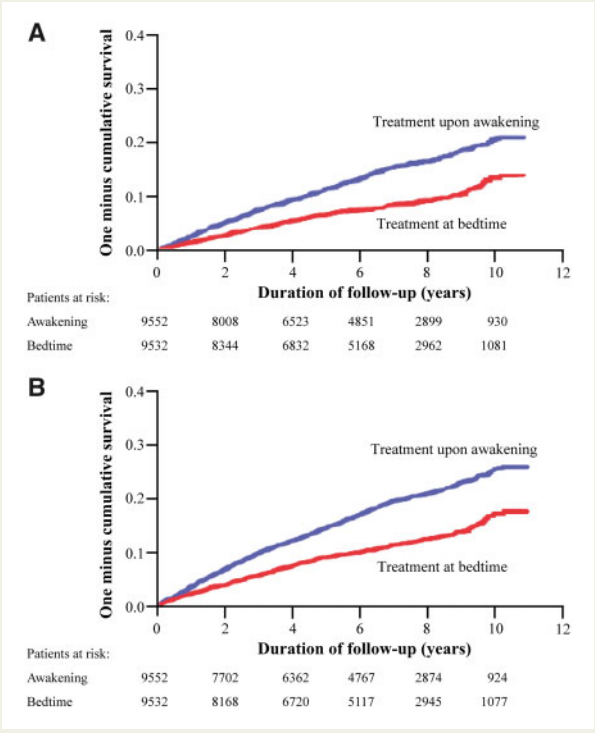



**Figure 3** Kaplan–Meier cumulative hazard curves for cardiovascular disease outcome as a function of hypertension treatment-time regimen (either upon awakening or at bedtime). (*A*) Cardiovascular disease outcome: composite of cardiovascular disease death, myocardial infarction, coronary revascularization, heart failure, and stroke; log-rank: 140.1, $P < 0.001$. (*B*) Total cardiovascular disease events: composite of cardiovascular disease death, myocardial infarction, coronary revascularization, heart failure, stroke, angina pectoris, peripheral artery disease, and transient ischaemic attack; log-rank: 174.0, $P < 0.001$.

control and enhanced sleep-time relative BP decline towards the more normal dipper BP pattern. One could, thus, conclude that the significant 45% reduction in CVD outcome achieved by ingestion of the entire daily dose of ≥1 BP-lowering medications at bedtime, compared with ingestion of all such medications upon waking (*Take home figure*), is partly linked to better achievement of those novel therapeutic goals through improved targeting of underlying circadian rhythm-organized biological mechanisms.[5] As previously reported,[11] analysis of the adjusted HR of CVD outcome in terms of the attained asleep SBP mean at the last available evaluation per participant reveals significant risk reduction even when the sleep-time SBP mean is <103 mmHg. This suggests the potential requirement of a therapeutic target of <120 mmHg for the asleep SBP mean, especially for high-risk patient groups, [18] an issue under current prospective investigation within the Hygia network (ClinicalTrials.gov, number NCT03457168).

Beyond more effective ABP control, the bedtime therapeutic strategy was also associated with improved renal function—significantly lower serum creatinine and albumin/creatinine ratio with higher eGFR—and favourable redistribution of lipid profile—significantly lower LDL cholesterol and higher HDL cholesterol—(*Table 2*), all of which are well-recognized relevant biomarkers of CVD risk. Moreover, the lower HR of CVD events for patients of the bedtime treatment than those of the awakening-treatment regimen was documented as highly significant regardless of sex, age, hypertension treatment, baseline ABP level and patterning, and absence/presence of diabetes, CKD, and/or previous CVD event (*Figure 4*). Finally, in keeping with previous findings,[3] results document that bedtime hypertension therapy is at least as safe, and with similar patient compliance and adherence, than usual upon-waking therapy.

Other prospective trials have reported the effect on CVD risk of an evening/bedtime schedule of hypertension medications. The HOPE trial established that add-on bedtime ramipril, relative to placebo, therapy significantly reduced the primary outcome variables of CVD death, myocardial infarction, and stroke in a cohort of 9297 already treated high-risk individuals aged ≥55 years.[12] Interestingly, a small ABPM substudy found profound lowering of the night-time SBP/DBP by an average of 17/8 mmHg ($P < 0.001$ compared with placebo) that translated into significant increase by 8% of the sleep-time relative BP decline.[25]

The Syst-Eur trial, involving 4695 elderly persons with isolated SBP hypertension diagnosed by OBPM alone, found that evening CCB nitrendipine therapy, compared with placebo, reduced the primary endpoint of stroke by 42% ($P = 0.003$), CVD mortality by 27% ($P = 0.07$), and total CVD outcomes by 31% ($P < 0.001$).[13] The Syst-China trial of almost identical protocol reported that evening treatment reduced stroke by 38% ($P = 0.01$), total mortality by 39% ($P = 0.003$), CVD mortality by 39% ($P = 0.003$), and total CVD outcomes by 37% ($P = 0.004$).[14]

The prematurely terminated CONVINCE trial, however, showed no difference in the primary outcomes of myocardial infarction, stroke, or CVD death between the bedtime dosed COER verapamil—specifically formulated for ingestion at this time to achieve peak drug concentrations upon morning arising—and morning treatment with either atenolol or hydrochlorothiazide.[15] Bedtime ingestion of COER verapamil exerts significant reduction in morning BP but only limited reduction in asleep BP, as documented by White *et al.*,[26] who reported two-fold greater decrease in awake SBP/DBP mean than in asleep SBP/DBP mean, thereby increasing the incidence of the higher CVD risk non-dipper BP pattern. These findings suggest that awakening, rather than bedtime, should have been the preferred regimen of this special CCB formulation to properly achieve asleep BP reduction.

These evening/bedtime ramipril, nitrendipine, and COER verapamil trials lacked a corresponding comparator upon-waking treatment arm. Nonetheless, Roush *et al.*,[27] who compared the results of the evening/bedtime-treatment studies summarized above (including COVINCE that, as discussed above, cannot be considered a proper bedtime-treatment trial) with those of 170 trials included in an earlier meta-analysis involving hypertension medications always ingested in the morning,[28] found significant 48% better attenuation ($P = 0.008$) in relative risk of CVD events when hypertension medications were consistently ingested at bedtime than at morning. This substantiated enhanced protective effect of bedtime treatment is similar to the 45% reduction in CVD outcome of the Hygia Chronotherapy Trial reported herein (*Figure 2*). The findings of Sobiczewski *et al.*[29] are also relevant. They evaluated the influence of hypertension

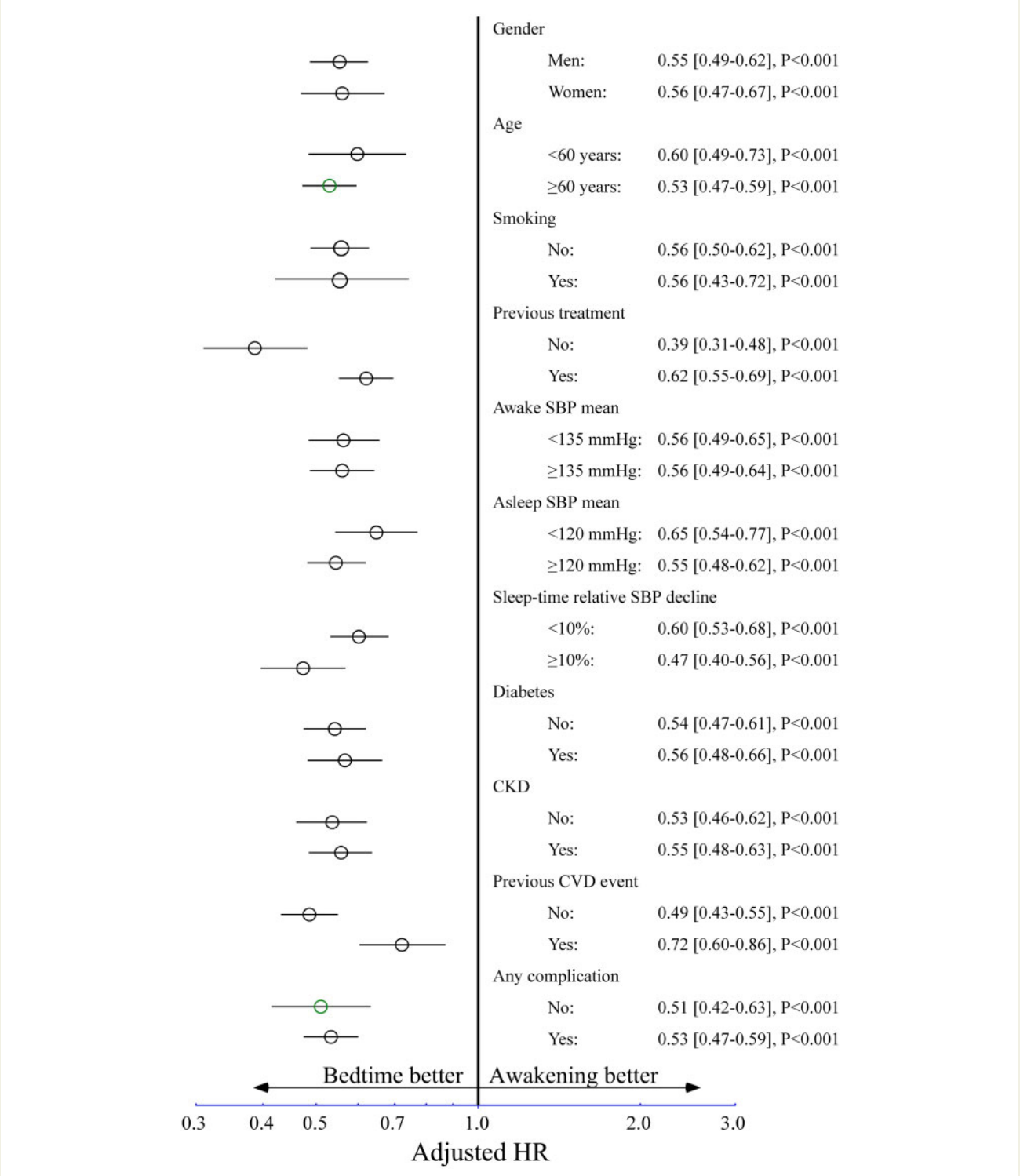
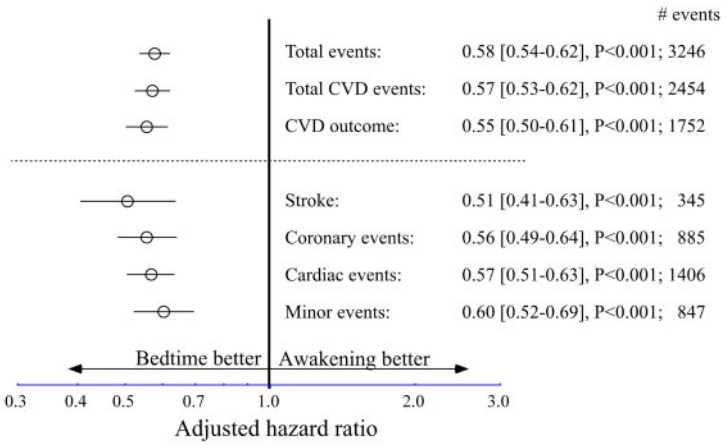



**Figure 4** Adjusted HR (95% CI) of the primary cardiovascular disease outcome (cardiovascular disease death, myocardial infarction, coronary revascularization, heart failure, and stroke) as a function of hypertension treatment-time regimen (either upon awakening or at bedtime) for participants categorized by potential markers of cardiovascular disease risk, i.e. sex, age, smoking, previous hypertension treatment, baseline ambulatory systolic blood pressure characteristics, and complications influencing prognosis of diabetes, cardiovascular disease, and/or previous cardiovascular disease event.




**Take home figure** Adjusted hazard ratio (95% CI) of cardiovascular events as a function of hypertension treatment-time (either upon awakening or at bedtime). Total events: Death from all causes, myocardial infarction, coronary revascularization, heart failure, ischaemic and haemorrhagic stroke, angina pectoris, peripheral artery disease, thrombotic occlusion of the retinal artery, and transient ischaemic attack. Coronary events: cardiovascular disease death, myocardial infarction, and coronary revascularization. Cardiac events: Coronary events and heart failure. cardiovascular disease-outcome: Cardiac events plus ischaemic and haemorrhagic stroke. Minor events: angina events, peripheral artery disease, thrombotic occlusion of the retinal artery, and transient ischaemic attack.

chronotherapy on mortality in 1345 patients with established coronary heart disease and who were assessed by 24-h ABPM. After the 6.6-year median follow-up, the Cox survival analysis revealed that the elevated asleep SBP/DBP mean [HR = 1.25, 95% CI (1.02–1.91), $P = 0.03$] and the absence of bedtime treatment [1.13, 1.01–1.45, $P = 0.04$] were the major markers of all-cause mortality. Finally, our findings also corroborate, and extend to the clinical primary care setting, the conclusions of the much smaller single-centre MAPEC study, the only previous properly randomized trial evaluating the effects of bedtime treatment vs. upon-waking BP-lowering treatment on CVD morbidity and mortality.[16]

The major limitation of the Hygia Chronotherapy Trial is that its findings require validation and extrapolation to other ethnic groups. In addition, our trial did not assign participants to specific hypertension medication classes or specific list of medications within each class; rather, treatment was chosen by each participating clinician respecting current clinical practice. This resulted in an unbalanced number of patients per medication class, although with a relatively balanced distribution among the two treatment-time groups in keeping with the PROBE design (*Table* 2). Nonetheless, differences in prescription rates among the different medication classes reflect current therapeutic preferences in the primary care setting, which in turn is one of the major advantages of our trial. Finally, use of a PROBE design might also be considered a limitation, although our trial had independent and blind adjudication of events; however, the PROBE design was specifically developed for conducting long-term outcome trials, being also the study design closest to routine clinical practice.

On the other hand, the Hygia Chronotherapy Trial has several strengths, mainly it: (i) provides results based on ABPM evaluations of 48 h, instead of the most common 24 h, duration to increase reproducibility of the ABP findings;[24] (ii) takes into consideration changes in ABP due to aging, treatment, and health status during follow-up through systematic periodic, at least annual, multiple 48 h ABPM assessments; (iii) utilizes a properly designed and validated patient diary, in the absence of wrist actigraphy as measured in all participants of the MAPEC study,[16] to ascertain the beginning and end of the activity/sleep spans to derive awake/asleep SBP/DBP means on an individualized basis, rather than relying on inaccurate daytime and nighttime values calculated assuming common and arbitrary fixed clock hours as described in most of the studies reporting apparent lack of benefit of bedtime treatment on asleep BP control[1]; (iv) defines hypertension as an inclusion criterion based solely on ABP measurements, as now recommended[18,30]; (v) prescribes changes in therapeutic intervention during follow-up to improve the control of asleep and awake ABP, instead of daytime OBPM; and (vi) allocates patients either to ingest BP-lowering medications upon awakening or at bedtime, i.e. according to the individualized rest/activity cycle that synchronizes the predictable-in-time 24 h changes in RAAS activation and other circadian mechanisms of BP regulation and patterning.[5] Finally, our trial constitutes a multicentre outcomes study conducted in the primary care setting; thus, the study is adapted to current medical practice by allowing physicians to prescribe, based on results of periodic 48 h ABPM evaluations of each patient, any single or combination BP-lowering medication of choice following established guidelines.

In conclusion, the prospective Hygia Chronotherapy Trial demonstrates ingestion by hypertensive patients of the entire daily dose of ≥1 prescribed BP-lowering medications at bedtime compared with ingestion as usual practice of all such medications upon waking results in both significantly improved asleep ABP control and significantly reduced CVD morbidity and mortality. It also demonstrates that the safety of the bedtime hypertension therapeutic scheme is similar to the more common awakening one, a finding consistent with previous publications reporting that bedtime compared with morning BP

therapy significantly improves ABP reduction without any increase in adverse effects.[3]

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**Conflict of interest:** none declared.

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